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Subsequent Cancer in Patients With Chronic Lymphocytic Leukemia—A Possible Immunologic Mechanism

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ABSTRACT—Among 4,869 patients with chronic lymphocytic leukemia (CLL) from the series of the End Results Program of the National Cancer Institute, Bethesda, Maryland, second primary cancers developed in 234 patients, compared to 204.9 expected. The risk was significantly elevated for malignant melanoma, soft-tissue sarcomas, and lung cancer. The frequency of rectal cancer was also elevated, but not significantly. The excess risk for these specific sites persisted throughout the period of follow-up, suggesting a susceptibility state that complicated the leukemic process rather than suggesting methodologic, diagnostic, or therapeutic effects. Immunologic defects in CLL may be involved in the etiology of excess risk for these sites, because a similar array of nonlymphoid tumors was seen following therapeutic immunosuppression among renal transplant recipients.—J Natl Cancer Inst 61: 337-340, 1978.

For nearly 100 years, since Whipham's case report linked CLL with pancreatic carcinoma (*1*), debate has flourished as to whether patients with CLL are prone to SPC. In spite of a shift from isolated case reports to statistical studies, this question remains unresolved. Most prior studies have been limited by small numbers of cases, inadequate comparison groups, biases related to hospital referral patterns, or more scrupulous follow-up of cancer patients. In the present study, a large national series of CLL patients has been utilized to evaluate the risk of developing SPC.

METHODS

The End Results Program of the National Cancer Institute provided survival data on patients with cancer diagnosed in over 100 hospitals of various types from different parts of the United States (*2*). Included were 4,869 white patients with CLL diagnosed between 1935 and 1971. Those developing a SPC *subsequent to* the diagnosis of leukemia were identified. Ascertainment of SPC began simultaneously with the diagnosis of CLL. From these patients the following data were abstracted: sex, age, year of diagnosis, age and year of entrance into the End Results Program, time elapsed since the diagnosis of CLL, tumor site, and histology. All CLL patients were stratified by initial course of therapy (radiation, chemotherapy, corticosteroids, and combinations thereof) to assess the possible role of treatment in the development of second tumors. The SPC was never the reason for initial referral into the system.

Expected numbers of cancers for all sites combined (excluding nonmelanoma skin cancers, which are not ascertained by the End Results Program) and for 21 specific sites were generated by application of the age, sex, and time-specific incidence rates from the general population to the corresponding person-years of follow-up accrued by the CLL patients. The rates used were from the Connecticut Tumor Registry (*3*). Person-years were accumulated from the diagnosis of CLL to the diagnosis of SPC, date of death, or closing date of the study (December 1972), whichever came first. Patients lost to follow-up were removed from the study in the year they were last known to be alive.

The strength of association was measured by the exact 95% CI around the ratio of observed to expected cases, referred to as the RR. If the lower limit of the CI did not include 1.0 (no association), the RR was considered significantly increased at the $P<0.05$ level.

RESULTS

From 1935 through 1971, 3,094 white males and 1,775 white females with CLL were reported to the End Results Program. This group accrued 16,584 person-years of observation, a mean of 3.4 years per person. As shown in table 1, SPC developed in 234 patients compared to 204.9 expected (RR=1.1; CI=1.0-1.3). The difference in both sexes was due primarily to excesses of malignant melanoma, soft-tissue sarcomas, lung cancer, and rectal cancer.

Malignant Melanoma

Melanoma developed in 9 patients compared to 1.34 expected (RR=6.7; CI=2.9-12.2). In table 2, the cases are stratified by treatment modality. Among untreated patients with CLL, a threefold increase of melanoma was found (CI=0.4-12.0), whereas the point estimate of RR among treated patients was 14.4. Thus, although the CI overlapped, the RR for treated patients fell outside the 95% CI of the RR for untreated patients, which suggested a possible increase in melanoma risk among CLL patients receiving therapy. In addition, the RR was elevated throughout follow-up: 7.8 in the first 2 years, 6.5 in the third to fourth years, and 5.8 subsequently. The risk was greater in patients with CLL

ABBREVIATIONS USED: CI=confidence interval(s); CLL=chronic lymphocytic leukemia; RR=relative risk(s); SPC=second primary cancer(s).

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TABLE 1.—*Observed numbers and relative risks of SPC in End Results CLL series*

Tumor site[a]	SPC						
	Male		Female		Total		
	Observed	RR	Observed	RR	Observed	RR	95% CI
Melanoma	6	7.8	3	5.3	9	6.7	2.9–12.2
Connective tissue	2	2.2	5	11.5	7	5.3	2.2–11.1
Lung	27	1.4	6	2.9	33	1.5	1.1–2.1
Rectum	15	1.6	8	1.8	23	1.6	1.0–2.5
Colon	18	1.2	10	0.9	28	1.0	0.7–1.5
Stomach	10	0.8	2	0.4	12	0.7	0.4–1.3
Pancreas	6	1.1	1	0.4	7	0.9	0.4–1.8
Esophagus	3	0.8	1	2.3	4	1.0	0.3–2.6
Larynx	4	1.3	0	—	4	1.3	0.3–3.2
Bladder	7	0.7	1	0.4	8	0.7	0.3–1.3
Non-Hodgkin's lymphoma	2	1.2	2	1.4	4	1.3	0.4–3.4
Breast	0	—	16	1.0	—	—	0.6–1.7
Ovary	—	—	4	1.3	—	—	0.4–3.4
Prostate gland	28	1.1	—	—	—	—	0.7–1.6
All other	24	0.8	23	1.1	47	0.9	0.7–1.3
Total	152	1.1	82	1.2	234	1.1	1.0–1.3

[a] Specific data presented for those sites at which 4 or more cancers occurred.

diagnosed before 1955 and in patients over 60 years of age at diagnosis. By cross-tabulating these variables, we found that all three factors (diagnosis prior to 1955, ≥60 years of age, and treatment) appeared to contribute independently to the increased risk of melanoma. Because of the small numbers involved, we could not assess the relative contribution of each factor.

Connective Tissue Neoplasms

This category includes all sarcomas except those of the bone. Seven tumors were observed (3 fibrosarcomas, 2 leiomyosarcomas, 1 liposarcoma, 1 angiosarcoma) compared with 1.33 expected (RR=5.3; CI=2.2-11.1). The excess was greater in females than males. Untreated patients had an elevated risk, with no additional increase associated with therapy (table 2). Three tumors occurred in the first year of follow-up (RR=10.0), 2 in the second (RR=9.3), 2 in the third (RR=11.6), and 1 thereafter.

TABLE 2.—*Observed numbers and relative risks of selected SPC that are in End Results CLL series stratified by treatment modality*

Type of SPC	Initial CLL treatment modality	SPC		
		Observed	RR	95% CI
Melanoma	None	2	3.2	0.4–12.0
	Chemotherapy	3	12.0	3.0–43.8
	Radiation	4	16.8	5.4–51.2
	Corticosteroids	0	—	—
Connective tissue neoplasms	None	5	7.8	2.7–19.4
	Any treatment[a]	2	2.9	0.3–10.3
Rectal cancer	None	12	1.8	0.9–3.1
	Chemotherapy	7	2.0	0.8–4.2
	Radiation	4	1.2	0.3–3.0
	Corticosteroids	1	0.6	0.01–3.5
Lung cancer	None	16	1.6	0.9–2.5
	Chemotherapy	10	1.6	0.7–2.9
	Radiation	5	1.0	0.3–2.4
	Corticosteroids	3	1.3	0.3–3.8

[a] Insufficient numbers of cases to meaningfully subdivide this category.

Lung Cancer

Lung cancer occurred in 33 patients compared with 21.88 expected (RR=1.5; CI=1.1-2.1). The excess was greater in females than males and was confined to patients with CLL diagnosed before they were 70 years of age. The RR was 1.6 among untreated patients, with no further increment in risk in any of the treatment groups (table 2). The RR was 0.7 for patients with CLL diagnosed prior to 1955 and rose to 1.5 between 1955 and 1964 and 1.7 after 1964. However, the risk of lung cancer diminished as the length of follow-up increased (RR=2.2 in the first year, 1.5 in the second to third years, 1.3 in the fourth to sixth years, and 1.0 thereafter). Cross-classification of tumors by length of follow-up and year of admission revealed that, throughout follow-up, the RR was elevated and constant among patients admitted prior to 1965. The apparent decrease in RR during follow-up for the total group was accounted for entirely by a sharply decreasing trend in RR among patients admitted after 1965. The distribution of histologic types (epidermoid carcinoma, 46%; adenocarcinoma, 21%; small cell carcinoma, 6%; and unspecified carcinoma, 27%) resembled the cell-type pattern for all lung cancers reported to the End Results Program.

Colorectal Cancer

Large bowel cancer developed in 51 patients compared to 40.6 expected (RR=1.3; CI=0.9-1.6). When analyzed by site, the elevated risk was limited to rectal cancer: 23 cases versus 14.02 expected (RR=1.6; CI=1.0-2.5). This excess occurred in untreated patients and was not further increased by therapy. The risk fluctuated

during follow-up (RR=2.4 in the first year, 0.9 in the second through fourth years, and 1.9 thereafter).

Other Neoplasms

For several other sites the risk exceeded expectation, but the numbers were too small for further analysis. These included cancers of the lip (2 cases, RR=1.6), tongue (3 cases, RR=2.4), salivary glands (2 cases, RR=3.4), Hodgkin's disease (2 cases, RR=2.4), and non-Hodgkin's lymphoma (4 cases, RR=1.3). None of these RR were statistically significant.

DISCUSSION

Seven statistically based studies of SPC developing in patients with CLL (*4-10*) have been published. Of these, six reported a significantly increased risk for all cancers combined, with RR estimates ranging from 1.2 to 4.0. In the seventh, a 30% excess for all cancers was found, but the difference was not statistically significant (*10*). Most surveys have reported an increased risk of nonmelanoma skin cancer, even after corrections were made for the underreporting of these tumors in the general population (*5*). The evidence that CLL predisposes to other cancers is less complete, although some studies have suggested an increased risk for cancers of the lung and large bowel (*7, 9*).

In this large series of CLL patients, there was a 10% excess of SPC, *excluding* nonmelanoma skin cancers, which are not ascertained by the End Results Program. The increase resulted from significant excesses of malignant melanoma, soft-tissue sarcomas, and lung cancer. The risk of rectal cancer was increased, but not significantly. For all four sites the excess risk affected *a*) both males and females, *b*) untreated patients as well as treated patients, and *c*) patients throughout all stages of follow-up.

Because of the rarity of malignant melanoma, it is unlikely that previous surveys covering far fewer CLL patients would have identified any excess. One study suggested a proportionate increase in all types of skin cancer including melanoma, but the numbers involved were small (*5*). In our series, a trend toward higher risk following treatment, including radiotherapy, was observed. Melanoma has been clearly linked to UV radiation, but not to X-irradiation (*11*), and, from the available data, we could not determine if any tumors arose in the radiation field. Soft-tissue sarcomas are also rare and not previously reported in association with CLL. Ionizing radiation may induce sarcomas (*12*), but the risk among radiation-treated patients in this study was not greater than that among untreated patients.

A predisposition to lung cancer was suggested in two previous surveys of CLL patients (*5, 9*). In our study the excess risk was mainly in patients with CLL diagnosed in recent years. This trend cannot be explained by the rising incidence of lung cancer in the general population, because time-specific incidence rates were used to calculate the expected number of cases. Although the treatment of CLL has become more aggressive recently (with more patients receiving combination chemotherapy or chemotherapy with irradiation), stratification of risk by year of admission and treatment modality failed to implicate any specific form of therapy. A decline in lung cancer RR during the follow-up of patients admitted in the most recent time period was noted, an observation for which we have no explanation. Finally, an increased risk of large bowel cancer was suggested by one report (*9*), but in our study the excess was limited to rectal cancer.

By analysis of the risk of SPC as a function of length of follow-up, it may be possible to establish which of several factors contribute to or simulate an increased risk. If the excess risk remains fairly constant throughout the period of follow-up, an intrinsic association between the 2 tumors may exist (e.g., a common etiology or tumor-associated abnormality predisposing to a second tumor). An initial interval of no excess, followed by increasing risk, suggests an effect of therapy. When the excess risk is limited to the first year or two, an ascertainment bias should be suspected because of close medical attention after the diagnosis of the first tumor. In our study, the elevated risk of melanoma persisted throughout follow-up, which suggests an intrinsic association with CLL. A similar mechanism may explain the excess of soft-tissue sarcomas and lung cancers during the first 3-6 years of follow-up. The absence of increased risk late in follow-up may be an indicator of disease severity, because patients with shorter survival usually have more aggressive leukemia. Rectal cancers clustered in the first year (perhaps related to the diagnosis of occult tumors on routine rectal examination), followed by a short period of no excess, which in turn was followed by a persistently elevated risk. This pattern suggests that at least some early rectal cancer cases were diagnosed because of close medical scrutiny, but that the overall excess is real and unrelated to treatment, diagnostic, or statistical biases.

In contrast to other immunodeficiency states (*13, 14*), we did not observe a significantly increased risk of lymphoma following CLL. Studies with lymphocyte surface markers suggest that in CLL, as in other lymphoproliferative tumors, the lymphoid cell line is already committed; the large-cell lymphomas that occasionally supervene in the terminal stages of CLL (Richter's syndrome) originate from the same clone of cells giving rise to CLL (*15*). Moreover, the diagnosis of lymphoma may be nearly impossible to make in a patient with CLL, because the histologic findings in well-differentiated lymphocytic lymphoma are indistinguishable from those in CLL involving extrahematopoietic sites (*16*).

Preliminary analysis was made of the End Results Program data for the four neoplasms associated with CLL and revealed no excess risk of leukemia *following* the diagnosis of these tumors. Thus the association is one-way. This argues against a common etiology and suggests that a susceptibility state associated with CLL may underlie the development of SPC. An etiologic

role for CLL's defective cellular and humoral immunity (*17–20*) is consistent with the recent observation that renal transplant recipients are prone not only to lymphoma and squamous skin cancer, but also to melanoma, soft-tissue sarcomas, and lung cancer (*21*). The clustering of lung cancer and soft-tissue sarcomas among CLL patients who died early in the course of their disease suggests that these patients had the most severe leukemia and, presumably, the most severe immunologic impairment. The early appearance of excess SPC risk in CLL is also analogous to the renal transplant experience (*22*). These data suggest that certain nonlymphoid tumors may result from impaired immunologic surveillance.

REFERENCES

(*1*) WHIPHAM T: Splenic leukemia with carcinoma. Tr Pathol Soc London 29:313-321, 1878

(*2*) CUTLER SJ, LATOURETTE HB: A national cooperative program for the evaluation of end results in cancer. J Natl Cancer Inst 22:633-646, 1959

(*3*) State Department of Health: *Cancer in Connecticut: 1935-1962 and 1966-1968* (Eisenberg H, ed). Hartford: State of Connecticut, 1971

(*4*) GUNZ FW, ANGUS HB: Leukemia and cancer in the same patient. Cancer 18:145-152, 1965

(*5*) BERG JW: The incidence of multiple primary cancers. I. Development of further cancers in patients with lymphomas, leukemias, and myeloma. J Natl Cancer Inst 38:741-752, 1967

(*6*) MORIARTY M: Skin carcinomata and chronic lymphatic leukemia—an association. J Irish Med Assoc 67:177-180, 1974

(*7*) NEWELL GR, KREMENTZ ET, ROBERTS JD, et al: Multiple primary neoplasms in blacks compared to whites. I. Further cancers in patients with Hodgkin's disease, leukemia and myeloma. J Natl Cancer Inst 52:635-638, 1974

(*8*) MANUSOW D, WEINERMAN BH: Subsequent neoplasia in chronic lymphocytic leukemia. JAMA 232:267-269, 1975

(*9*) MOAYERI H, HAN T, STUTZMAN L, et al: Second neoplasms with chronic lymphocytic leukemia. NY State J Med 76:378-381, 1976

(*10*) STAVRAKY KM, WATSON TA, WHITE DF, et al: Chronic lymphocytic leukemia and subsequent cancer in the same patient. Cancer 26:410-414, 1970

(*11*) EMETT EH: Ultraviolet radiation as a cause of skin tumors. CRC Crit Rev Toxicol 2:211-255, 1973

(*12*) LOUITT JF: Malignancy from radium. Br J Cancer 24:195-207, 1970

(*13*) BRINCKER H, WILBEK E: The incidence of malignant tumours in patients with respiratory sarcoidosis. Br J Cancer 29:247-251, 1974

(*14*) KERSEY JH, SPECTOR BD, GOOD RA: Primary immunodeficiency and cancer: The immunodeficiency-cancer registry. Int J Cancer 12:333-347, 1973

(*15*) BROUET JC, PREUD'HOMME JL, FLANDRIN G, et al: Membrane markers in "histiocytic" lymphomas (reticulum cell sarcomas). J Natl Cancer Inst 56:631-633, 1976

(*16*) BRAYLAN RC, JAFFE ES, BERARD CW: Malignant lymphomas—current classification and new observations. Pathol Annu 5:213-270, 1975

(*17*) ULTMAN JE, FISH W, OSSERMAN E, et al: The clinical implications of hypogammaglobulinemia in patients with chronic lymphocytic leukemia and lymphocytic lymphosarcoma. Ann Intern Med 51:501-516, 1959

(*18*) MILLER DG: Patterns of immunological deficiency in lymphoma and leukemias. Ann Intern Med 57:703-716, 1962

(*19*) CONE L, UHR JW: Immunological deficiency disorders associated with chronic lymphocytic leukemia and multiple myeloma. J Clin Invest 43:2241-2248, 1964

(*20*) BLOCK JB, HAYNES HA, THOMPSON WL, et al: Delayed hypersensitivity in chronic lymphocytic leukemia. J Natl Cancer Inst 42:973-980, 1969

(*21*) HOOVER R: Effects of drugs—immunosuppression. *In* Origins of Human Cancer. Cold Spring Harbor Conferences on Cell Proliferation (Hiatt H, Watson JD, Winston JA, eds), vol 4. New York: Cold Spring Harbor Laboratory, 1977, pp 296-301

(*22*) HOOVER R, FRAUMENI F JR: Risk of cancer in renal transplant recipients. Lancet 2:55-57, 1973